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The combined use of Tc-99m-phosphate and Ga-67-citrate imaging in the diagnosis of acute osteomyelitis in children

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ABSTRACT

This investigation was undertaken to determine the value of combined bone (technetium-99m-MDP) and gallium-67-citrate imaging in a selected group of children with complicated clinical situations.

Thirty-one children were evaluated for suspected osteomyelitis by bone scan followed within four days by a gallium scan. These 31 children represented a subpopulation in whom the Tc-99m MDP bone scan, for a variety of reasons, is known to be potentially unreliable in the diagnosis of acute osteomyelitis. Analysis was retrospective. Eight children had acute osteomyelitis by strict criteria while 23 did not. The bone scan successfully identified 5 of the 8 children with osteomyelitis, but was positive in 10 of the other 23 children. The gallium scan correctly identified all 8 children with osteomyelitis, however was positive in 7 of the other 23 cases. The gallium scan was significantly less specific when the suspected lesion was in the extremities as compared with central locations. Causes of positive gallium scans in the absence of osteomyelitis included fracture and juvenille rheumatoid arthritis.

Combined use of gallium and bone scanning increased the accuracy of the scintigraphic diagnosis of acute osteomyelitis in the population studied. Both tests may, however, be abnormal in conditions other than osteomyelitis.

This thesis is dedicated,

with love,

to Linda

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1

INTRODUCTION

The differential diagnosis of acute hemotogenous osteomyelitis from soft tissue or joint inflammation in children is often difficult. The radionuclide bone scan, performed using technetium-99m-labeled phosphate compounds has been useful. Initial studies reported sensitivities approaching 100% (19,26,27,45,46,47,50,72). More recent studies, however, suggest somewhat lower sensitivity (9,23,24,68). The sequential use of Tc-99m-phosphate and Ga-67 scans has been shown useful in the detection of acute osteomyelitis both in adults (46,61,66) and in children (47,32). The combined study is most useful when the bone scan is normal and the suspicion of osteomyelitis is high or when the bone scan is positive but an alternative cause of increased bone turnover exists. In this retrospective study the relative sensitivities and specificities for the bone scan and gallium scan were evaluated in a population of children suspected of having acute osteomyelitis who underwent both scans.

2

REVIEW OF THE LITERATURE

2.1 ACUTE HEMATOGENOUS OSTEOMYELITIS

Acute Hematogenous Osteomyelitis is a disease that is characteristically seen in children, with over 85% of cases in patients less than sixteen years of age (77). Classically, symptoms begin abruptly, with the child appearing toxic and pale. Early manifestations include local tenderness over the affected bone along with high fever (although either may be absent). An area of swelling and erythema in the region of tenderness may be found later in the course of the disease (41). In contrast, osteomyelitis in the neonate often presents with minimum or absent clinical symptoms. Tissue edema, decreased movement of a limb, or adjacent joint effusion may be the only findings in up to 70% of cases (76).

There are several laboratory findings which support the diagnosis of osteomyelitis. The total white blood cell

count is helpful if elevated, however it is often normal in children with early disease. The erythrocyte sedimentation rate, in contrast, is usually elevated with osteomyelitis and, although nonspecific, may be used to help in diagnosis as well as to follow the progress of treatment. The blood culture is usually positive early in the course of the disease, and the presence of pus or the growth of microorganisms from bone aspirate or biopsy is conclusive evidence of osteomyelitis. Culture of blood and bone aspirate or biopsy should be performed before the institution of antibiotic therapy if possible, both to increase the yield of bacterial growth and to determine the appropriate antimicrobial agent for treatment. A chest radiograph and tuberculin test can also be useful in determining the etiologic agent in children with subacute or chronic osteomyelitis (7).

Although the classic radiologic changes of periosteal new bone formation and bone destruction are not seen for 10 to 14 days after the onset of osteomyelitis, several earlier changes may be observed. The first soft tissue change, noted around the third day of the illness, consists of local, deep soft tissue swelling adjacent to the metaphysis, which is recognized by the displacement of the lucent deep muscle fat plane away from the bone. The next change observed occurs several days later; the lucent planes

between muscles are obliterated beginning with the deep planes and slowly spreading superficially. Superficial subcutaneous soft tissue edema is the last change noted before rarefaction of the metaphysis becomes apparent. If the osteomyelitis is allowed to progress, destruction of the bone can be observed, along with periosteal new bone formation. Eventually, islands of dead bone, termed sequestra, will become evident (14). The early soft tissue changes are subtle, and the radiographic differentiation of osteomyelitis from soft tissue infection is often not possible.

In otherwise healthy children the causative organism of osteomyelitis is *Staphylococcus aureus* in 60 to 70% of cases. Salmonella species have long been noted as pathogens in patients with sickle cell SS or SC hemoglobinopathies (77). *Pseudomonas aeruginosa*, rarely seen in the general population, has recently been noted as the offending agent in the majority of intravenous drug abusers with this disease (76). Osteomyelitis in the neonate is often due to group B Streptococcus and *E. coli* in addition to *Staphylococcus aureus* (*76*).

The high incidence of acute hematogenous osteomyelitis in the pediatric population is a consequence of the pathophysiology of the disease. Acute hematogenous

osteomyelitis most often affects rapidly growing bone, with the metaphysis of long bones frequently infected. The nutrient blood supply of the diaphysis divides in the region of the epiphyseal growth plate into sharp capillary loops which then empty into a venous sinusiodal network with sluggish blood flow. These loops are non-anastomotic end-branches of the nutrient vessels; any obstruction by bacteria or thrombi may quickly lead to small areas of ischemic necrosis. In the pediatric age group, pre-existing bacteremia from a variety of causes can lead to a seeding of the metaphysis in the region of slowed blood flow. Infection can spread laterally along the growth plate, eventually breaching the cortex and elevating the loose periosteum. As the osteomyelitic process continues, the high pressure of subperiosteal and intraosseous pus can cause compromise of the vascular structures, leading to areas of infarction and necrosis that form islands of avascular bone (73).

This is in contrast to osteomyelitis in the older adolescent or adult, in whom the epiphysis has fused, allowing infection to spread to the epiphyseal region of the bone and potentially into the joint space. Also, the tight apposition of the periosteum to the cortex in the mature bone prevents the magnitude of the periosteal reaction seen in the younger population (77). Osteomyelitis in the

neonate differs from that in the older pediatric population in several respects. Bone infection in these patients rapidly crosses the epiphyseal growth plate, leading to mutilating septic arthritis. Also, osteomyelitis is multifocal in 40% of cases in the newborn (76), as compared to 13% of cases in the total population (77).

Treatment of osteomyelitis relies on a combination of medical and surgical management. The mainstay of medical therapy has been a four to six week course of high dose parenteral antibiotics selected for maximum bacteriocidal activity against the specific offending organism (77). Trials designed to decrease the cost and psychological impact of an extended hospitalization have been done, however. An investigation utilizing a five to nine day course of intravenous antibiotics followed by fourteen to twenty-six days of orally administered antibiotics has resulted in a 95% cure rate, although this therapy is useful only for selected cases (76).

Although antibiotic therapy alone can cure acute hematogenous osteomyelitis if given before extensive bone necrosis has occured, it is presently believed that organisms residing in the infarcted bone of sequestra can cause flareups as late as 50 years after the initial infection (76). Thus, surgical decompression, abscess

drainage, and debridement are considered important in the prevention of extensive bone necrosis secondary to high intraosseous pressure, which may lead to the development of chronic disease. Complete removal of necrotic tissue is desirable, and resultant empty cavities may be filled with skin flaps, muscle flaps, or temporarily with synthetic materials (76). When treatment is prompt and thorough, permanent disability can be avoided (32).

2.2 TECHNETIUM-99M PHOSPHATE IMAGING

The use of radionuclides for the external imaging of bone in the human was initially attempted by Bauer and Wendeberg; in a study published in 1959, seventy-five patients were injected with either the radioisotope Sr-85 or Ca-47. Although in this early study fracture, slipped upper femoral epiphysis, malignancy, Paget's disease, and osteomyelitis were evaluated, the large absorbed dose of radiation to the bone, 4.4 rads from Ca-47 and 3.4 rads from Sr-85 (approximations based on a seventy-kilogram man), restricted the use of external radionuclide bone imaging to cases of malignancy (6). Other radioisotopes with better physical characteristics were evaluated during the following decade. Myers introduced Sr-87m in 1960 (55) with a much lower absorbed radiation dose, ranging from 0.1 to 0.6 rad to the bone, and a much shorter interval between radionuclide administration and imaging (2 to 6 hours as compared to 2 to 14 days for Sr-85), however its short half-life of 2.8 hours along with a slow clearance from blood rendered it unsatisfactory for imaging (57). A much better radioisotope for imaging was F-18, introduced in 1962 by Blau *et al* (10). Its radiation dosage of only 1.8 rad to the bone, short interval between injection and imaging resulting from rapid plasma clearance, and selective deposition in the bone

were advantages over the earlier agents. This imaging agent fell into disuse with the advent of the technetium phosphate compounds, however, because of its high cost, limited availability, and short half life (57).

Investigation into the use of external bone imaging in non-malignant disease in children began after the introduction of technetium-99m-polyphosphates by Subramanian and McAfee in 1971 (67). The shorter half-life of technetium-99m and its lack of beta-radiation, with a total absorbed radiation dose of only 0.5 to 0.7 rad to the bone, combined with the advent of the gamma camera allowing better spatial resolution allowed bone scintigraphy in children to advance (57). Many different polyphosphate and phosphonate technetium-99m radiopharmaceuticals have been used, however Tc-99m-MDP is the current agent of choice.

The quantitative uptake of Tc-99m-MDP in bone is determined by several factors. The distribution of Tc-99m-MDP within bone is primarily a consequence of of local blood flow with elements of neo-vascularity, neurovascular regulation, and capillary permeability contributing to the increased activity observed in areas of inflammation and increased bone metabolism. Once within the bone the technetium-99m-MDP is adsorbed strongly to the surface of the calcium hydroxy-apatite crystal. Newly mineralized bone and bone

undergoing active resorption present an increased crystal surface area and further add to the strong uptake noted in regions of increased metabolic activity (16).

The earliest investigations of the use of technetium-99m radiopharmaceuticals in the evaluation of osteomyelitis were extremely encouraging, however the criteria for proof of osteomyelitis were often inconclusive. Letts *et al* in 1975 reported a study of twenty children, 13 months to 13 years of age, with suspected but not clinically apparent osteomyelitis. The children were imaged with technetium-99m-polyphosphate utilizing rectilinear scanner, resulting in a sensitivity of 100% and a specificity of 83% (45). Later that year, Duszynski *et al* reviewed 42 pediatric patients and directly compared radiography to scintigraphy. Utilizing Tc-99m-Sn-pyrophosphate and either a gamma camera or a rectilinear scanner a sensitivity of 95% and a specificity of 96% were obtained, while conventional radiographs showed only one of the twenty patients with osteomyelitis to have positive bony findings (19).

Blood pool imaging, an image obtained about one to five minutes following radionuclide injection, provided a new method to discern any abnormality in blood distribution suggesting underlying pathology. Its application in the diagnosis of osteomyelitis versus cellulitis was introduced

in 1975 by Gilday *et al* in a prospective study of 134 children with suspected osteomyelitis. Blood pool images of the suspected areas were obtained immediately after injection of technetium-99m-methylene diphosphonate, followed by one or two hour delayed bone images. A gamma camera was used in all cases. Osteomyelitis was substantaited by inconclusive criteria, with over half of the children given the diagnosis of osteomyelitis on the basis of prompt response of symptoms to antibiotic therapy without corroborating cultures or radiographic changes. The sensitivity of the bone scan in this series was 99%, and the specificity was 100%, as compared with conventional radiography which yielded a sensitivity of only 45%. The authors concluded that blood pool imaging was a helpful addition to the static bone scan in the differentiation of osteomyelitis from cellulitis and septic arthritis (27).

This conclusion was supported by Majd and associates in a retrospective evaluation of sixty-five children between the ages of eight days and sixteen years with suspected osteomyelitis. The blood pool and static views were obtained after injection of Tc-99m-diphosphonate, and proof of osteomyelitis was based on bone marrow aspirate culture, blood culture, or followup radiographic changes. One case was proven on clinical grounds alone. Osteomyelitis was confirmed in twenty-three of the children, of which twenty

had acute disease and three chronic. The bone scans were positive in all twenty-three cases, however one was falsely negative on presentation, but became positive one week later. Only three of the twenty patients with acute osteomyelitis had positive findings on initial radiographs, and nine with positive bone aspirate or blood cultures never went on to have radiographic changes. The scintigraphic studies for the patients with cellulitis, bone infarct, and septic arthritis are described as being characteristic of the particular disease in all cases (50).

Along with earlier diagnosis of osteomyelitis than possible with conventional radiography, the bone scan also allowed recognition of otherwise unsuspected foci of osteomyelitis and aided in the choice of a site for surgical aspiration or biopsy. The use of scintigraphy to localize areas of osteomyelitis for biopsy was suggested by Treves *et al* in a study of nine children, two to thirteen years of age, with suspected osteomyelitis. During imaging with Tc-99m-methylene diphosphonate a radioactive marker was placed over the bony abnormality; biopsy was then performed at the site of the marker in 7 of the nine patients. The scintigraphic diagnosis was correct in all 8 children with osteomyelitis, and in the one child without osteomyelitis. All but one child had adequate biopsy or followup radiographic proof of osteomyelitis. No initial radiographs showed evidence of bony abnormality (72).

During the same period it was recognized by many that an area of focally increased uptake was not the only pattern associated with acute osteomyelitis. Russin and Staab, in 1976, reported a case of a twenty month old boy who had a clinical picture consistent with osteomyelitis. Bone scan revealed an area of decreased uptake in the region of interest. On surgical exploration pus was found to be elevating the periosteum circumferentially, occluding the nutrient arteries of the area (63). Trackler *et al* reported a similar case in an eight year old with a discrete area of decreased uptake in the pubis and ischium on bone scan. Surgical exploration again was remarkable for large amounts of pus under high pressure elevating the periosteum over a grossly intact bone (71). In a larger series, Murray discussed several cases with diminished uptake on bone scan, with etiologies including osteomyelitis, septic infarction, septic arthritis, and sterile effusion (54).

The mechanisms proposed for the diminished uptake in acute osteomyelitis included local ischemia due to septic thrombosis of nutrient vessels and pressure necrosis from compromise of the microcirculation by sub-periosteal and intraosseous pus (54). After incision and drainage to relieve the pressure, an increase in radiotracer uptake was described, consistent with improvement in the microcirculation with renewed blood flow (71).

As early as 1977 it was noted that classical acute osteomyelitis could present not only with an abnormality in bone scan uptake, but also with a normal bone scan, as reported by Garnett *et al*. A bone scan performed five days after the onset of a clinical picture classic for acute osteomyelitis of the humerus in a previously healthy eleven year old boy revealed only a very slight increase in radiotracer accumulation in the bone distal to the suspected lesion, without any related soft tissue uptake. The clinical picture was convincing enough to warrant surgical exploration, which revealed a collection of subperiosteal pus as well as pus in the medullary cavity when the bone was drilled. Bone scans done on the eighth and nineteenth day of the illness showed evolving scintigraphic evidence of osteomyelitis with a more classical image of increased bone and soft tissue uptake. The explanation proposed to account for this atypical 'false negative' situation was similar to that for the 'cold lesions' discussed above. At some point the increase in the vascular bed and tracer accumulation could be balanced by increased perivascular pressure resulting in an almost normal radionuclide accretion (25).

Several studies also support the contention that the bone scan is not as infallable as the earliest studies suggested. Sullivan *et al* reviewed the bone scans of twenty-one

children with osteomyelitis proven by extremely strict criteria. Imaging was done with Tc-99m-pyrophosphate and a gamma camera, utilizing multiple views to image the total body as well as pinhole or converging collimators to image the area of interest. Of the twenty-one children, eleven had scintigraphic findings considered to be 'obvious' for osteomyelitis, four had subtle findings, four had scans considered 'normal', and two had images considered 'misleading'. Ten of these children underwent blood pool imaging, which was not found to be helpful in making the diagnoses (68). The findings of Sullivan and associates were supported by a smaller study in which Berkowitz and Wenzel imaged seven children with Tc-99m-MDP three to five days after the onset of symptoms. The bone scans were reported as normal in all cases. Each child was considered to have proven osteomyelitis, however the method of proof was lax, with two patients considered proven on the basis of a subsequent positive gallium scan alone, with negative followup radiographs and sterile blood and bone cultures. Furthermore, nothing can be deduced about the frequency of negative bone scans from the data presented, which were selected on the basis of negative bone scan findings in the presence of osteomyelitis (9).

A more recent study by Howie *et al* published in 1983 was undertaken with care to substantiate the final diagnosis.

290 patients between the ages of six weeks and thirteen years (average age six years) presented to the Adelaide Children's Hospital during the five year period ending in May 1981 with suspected osteomyelitis. Only those patients with surgical or radiographic evidence of osteomyelitis were included in calculations of scan accuracy. Technetium-pyrophosphate or Tc-MDP were used, and a gamma camera was utilized for imaging. Blood pool views were obtained in all patients. The sensitivity of the bone scan for this group was 89% and the specificity was 94%. The sensitivity of the plain radiograph for this group ranged from 5% at three days duration of symptoms to 100% at three weeks duration. Howie and associates concluded that if meticulous technique and two-phase scanning were utilized, the bone scan was highly sensitive and specific in the diagnosis of osteomyelitis in children (40).

In addition, Fihn *et al*, in 1984, studied 69 patients in an attempt to evaluate the impact of the bone scan on the diagnostic and therapeutic course of the patient. The method of proof was similar to that of Howie, with only surgical findings and subsequent radiographic changes considered as sufficient evidence of osteomyelitis. Technetium-MDP and a large field of view gamma camera were utilized to obtain static delayed images. The sensitivity was 79% and the specificity was 93% for the series overall,

however when equivocal positive and equivocal negative interpretations were allowed, 21% of them were false, compared to 5% of the definite interpretations. In evaluating the impact of the scintigraphic reading on the patient outcome, results of imaging were "unhelpful or misleading" more often in patients with high or moderate probability of osteomyelitis than in patients with a low pre-scan probability of osteomyelitis. These probabilities were determined on the basis of clinical data from chart review. In six cases the diagnosis was correctly altered in light of the imaging results, and in two case the diagnosis was incorrectly altered, resulting in one false negative and one false positive diagnosis. In those patients in whom scintigraphic results did not alter the pre-scan diagnosis, it increased diagnostic certainty significantly more often when osteomyelitis was absent than when it was present. Effect of the imaging results on therapeutic action was found in only 18% of the cases. The authors concluded that when osteomyelitis was considered unlikely, the bone scan was usually negative or falsely positive, and did not significantly alter treatment, while when probability of osteomyelitis was high, the bone scan results probably effected treatment positively in 41% of cases, but was unhelpful or misleading in 33% of cases (23).

The role of the bone scan in the evaluation of neonatal osteomyelitis has also been the subject of some controversy. The earliest study, conducted by Ash and Gilday, evaluated twenty-one neonates with the onset of suspected osteomyelitis before the age of thirty days. Substantiation of the presence of osteomyelitis included positive changes on followup radiographs, bone aspirate culture, blood culture, or CSF culture. Of the twenty sites of osteomyelitis in these ten neonates, 31.5% were positive on bone scan, 10.5% were equivocal, and 58% were falsely normal. No relationship was noted between the scan outcome and the duration of disease at time of scanning or the use of antibiotics before scanning (4).

In a study published two years later at the same institution, Mok, Reilly, and Ash investigated twenty-two infants presenting between 1970 and 1979. Osteomyelitis was considered proven by radiographic changes along with a postive culture of blood, joint fluid, or local tissue aspirate. Bone scans were obtained on presentation in ten infants, utilizing either Tc-polyphosphate or Tc-MDP. Seven of ten infants had abnormal bone scans, compared to 19 of 22 abnormal initial radiographs (86%). In seven of these abnormal radiographs, however, soft-tissue swelling was the only abnormality. This study concluded that the bone scan added no significant data when the radiograph is positive,

however in two infants initial radiographs were negative while scintigraphs were positive (53).

The most recent investigation was by Bressler, Conway, and Weiss, in 1984. Thirty-three children suspected of having osteomyelitis with the onset of symptoms at less than six weeks of age were evaluated. Proof of osteomyelitis was by culture of bone aspirate or radiograph in fourteen of the fifteen patients considered to have osteomyelitis. The remaining infant had a positive gallium scan along with growth of organisms from blood cultures. High resolution converging collimation and pinhole views were obtained for each infant. Thirteen of the fifteen patients with osteomyelitis had increased uptake at the sites of proven infection, while the remaining two infants had decreased radionuclide activity in the regions of interest. Of the twenty-five sites proven to be osteomyelitis, all showed abnormality on scintigraphy. Two of the fifteen patients with osteomyelitis had normal initial radiographs. These investigators concluded that bone scanning was more sensitive than radiography for detecting osteomyelitis in neonates when modern higher-resolution gamma cameras and magnification of all views are utilized (11).

2.3 GALLIUM-67 CITRATE AND SEQUENTIAL IMAGING

Radiogallium was initially investigated as a potential bone imaging agent. Edwards and Hayes were the first investigators to recognize and evaluate the use of gallium-67 citrate in imaging human soft tissue tumors (21). Its use in imaging inflammatory lesions was initially described by Lavender *et al* (44) and Littenberg *et al* (48). Once the use of gallium imaging in inflammatory processes was established, application to the difficult problem of diagnosing osteomyelitis was attempted. The capability of detecting the inflammatory process directly, rather than by inference as evidenced by increased bone blood flow or reparative activity (as with technetium-99m-phosphate compounds) offered the potential of improved specificity.

The localization of gallium-67 citrate to areas of inflammation is a consequence of its resemblance to the ferric ion. Gallium-67 is transported through the plasma bound to transferrin. The protein bound gallium-67 is then delivered assisted by the increased blood flow and vascular permeability within the inflammatory lesion. Lactoferrin, an iron binding protein found within the secondary granules of the neutrophil, is present at the inflammatory site in

high concentration as a result of neutrophil degranulation or death. Gallium is bound strongly to lactoferrin resulting in accumulation of the radionuclide within the lesion. Gallium is bound even more avidly by siderophores, iron-binding proteins present within bacteria. Uptake by bacteria and binding to siderophores further contributes to the increased gallium-67 activity observed at sites of infection (37,38,74).

In 1977 Lisbona and Rosenthall described the addition of the gallium scan to the technetium-99m-MDP scan in the evaluation of osteomyelitis. A study population of 40 adults and children with suspected inflammatory disease each underwent gallium-67-citrate imaging immediately following completion of a technetium-99m-MDP bone scan (the radionuclide was injected immediately after the bone scan and gamma camera images were obtained at 24 hours). Of the seventeen patients given the discharge diagnosis of active osteomyelitis, all had positive bone scans and gallium scans. The authors report that the gallium scan permitted differentiation between active and inactive chronic osteomyelitis as well as aiding in the detection of foci of osteomyelitis adjacent to the growth plate in children with subtle bone scan findings (46).

In another study later that year, Lisbona and Rosenthall evaluated thirty-eight children with septic arthritis, juxta-articular osteomyelitis, cellulitis, or a combination of these. Each patient underwent sequential scanning in the same manner described above; of the thirteen children subsequently given the discharge diagnosis of osteomyelitis eight had both bone and gallium scans positive while five children had positive gallium scans and negative bone scans. They concluded that the gallium scan was more sensitive than the bone scan, and hypothesized that this was most likely a result of the juxtaposed growth plate activity obscuring the metaphyseal osteomyelitic foci (47).

The distribution patterns and relative degrees of uptake for technetium-99m-MDP and gallium-67 citrate in osteomyelitis were investigated in several subsequent studies. Rosenthall and Lisbona observed forty-six adult patients with orthopedic prostheses or fixation devices who underwent sequential scanning in the evaluation of suspected complications. All patients studied had surgically violated bone, rendering the bone scan alone non-diagnostic in the investigation of suspected osteomyelitis. Comparison with the gallium image served to define three groups. All twelve of the patients with negative gallium images and either positive or negative bone scans had no evidence of inflammatory disease on followup. Sixteen patients with

positive gallium and bone scan images in a congruent spatial distribution were also free from infection. However, all eighteen patients with postive gallium and bone scans in an incongruent spatial distribution proved to have osteomyelitis, cellulitis, non-septic synovitis, or a combination of these (62).

Rosenthall *et al* further defined uptake patterns in a study published in 1982 in which 159 patients with an initial clinically suspected osteomyelitis were evaluated. Thirty-one patients were considered to have osteomyelitis as proven by local fluid or tissue culture, blood culture along with clinical evidence, biopsy histology, and/or progressive radiographic bone changes. Thirty-four more patients were considered to have a high probability of osteomyelitis based on clinical evidence alone. When the criteria for positivity were defined as a positive bone scan and moderate to intense gallium uptake in a congruent pattern, or an incongruent pattern with any intensity of gallium uptake, the sensitivity of the sequential study was 72% with a specificity of 86%. When the criteria for positivity disregarded the spatial pattern, however, and included all grades of gallium uptake, the sensitivity was 80% while the specificity fell to 72%. They concluded that much more confidence can be placed in the incongruent pattern of uptake, which implies an inflammatory condition superimposed on the underlying bone hyperemia (61).

Handmaker and Giammona published a study in 1984 evaluating thirty-seven children between the ages of two weeks and sixteen years admitted with suspected osteomyelitis, septic arthritis, or cellulitis. Each child underwent either a bone scan, a gallium scan, or both. The diagnosis of osteomyelitis was established in seventeen patients either by blood or tissue culture or by consistent surgical findings. Five of these patients had a positive gallium scan immediately following a negative bone scan, athough followup bone scans in three of them were positive. No child with osteomyelitis in this series had a negative gallium scan, and no mention of the congruent or incongruent spatial distribution of the uptake was made. The authors concluded that all normal or inconclusive bone scans in a child with suspected osteomyelitis should be followed by a gallium scan (32).

The above study is in contrast to an investigation published in the same year by Schauwecker *et al* comparing Tc-99m-MDP, Ga-67, and In-111 labeled granulocytes in the evaluation of suspected osteomyelitis complicating underlying diseases with increased bone metabolism. Of the 57 adult patients evaluated, 32 proved to have osteomyelitis by either histological and clinical findings (24 patients) or clinical findings alone (8 patients). In the total study population,

the gallium scan had a sensitivity of 100% and a specificity of 25%. When the gallium scan was more intense than the the bone scan, regardless of distribution, the sensitivity was only 14% with a specificity of 100%. When the distribution was disparate, however, the sensitivity was 24% with a specificity of 100%. The conclusion was reached that gallium-67 was very accurate when the scan was negative, the intensity was greater than that on bone scan, or the pattern of uptake was disparate to that on bone scan. In this series of patients with underlying bone abnormalities, however, only 28% of the study population fit into one of these three groups (64).

The efficacy of gallium imaging in the diagnosis of osteomyelitis was also evaluated experimentally utilizing the animal model developed by Norden (56). In 1975 Deysine *et al* showed that injected gallium-67 quickly localized to areas of bone that had undergone the instillation of a sclerosing agent along with an innoculum of *Staphylococcus aureus*, and remained present for up to 72 hours (18). The timing of the development of technetium-99m-MDP and gallium-67 citrate scan abnormalities was examined in two later experimental studies. Dye and others described gallium scan abnormalities present one week after innoculation in 44% of rabbits with experimental osteomyelitis, as compared to bone scan abnormalities in

only 11%. In the subsequent weeks 89% of the rabbits developed abnormalities in both scans, however in no case did the bone scan become positive before the gallium scan (20). Graham *et al* showed that two days following innoculation, two thirds of their animals had abnormal gallium scans while none had abnormal bone scans. On the third day following innoculation all animals had developed abnormalities on gallium scan, while only one third revealed bone scan abnormalities (29).

The use of gallium imaging in predicting the clinical course of osteomyelitis and response to treatment has been investigated both in the animal model and in the clinical setting. Graham and associates performed two experiments in which they gave antibiotic therapy to rabbits with osteomyelitis, obtaining gallium scans at intervals. In from forty to fifty-nine percent of the animals the gallium images reverted to normal during the course of treatment, and in none of these animals could bacteriological evidence of persistent infection be produced. Proof of infection was found in 58% to 72% of those animals with continued abnormal gallium images (28,30). The bone scan, however, remained positive in all animals at the end of treatment (30). From these experiments Graham's group concluded that although the bone scan yielded no useful information concerning the response of osteomyelitis to treatment, the gallium scan was a useful test in predicting the cure of osteomyelitis.

Kolyvas *et al* tested this hypothesis in a clinical setting in a study of ten children with acute osteomyelitis. Each child was treated with a minimum of six weeks of antibiotic therapy and underwent bone and gallium scans on presentation, after two to four weeks of therapy, and at the end of treatment. On clinical followup there were no treatment failures. Nine children showed a significant decrease in gallium uptake after two to four weeks of treatment, however the gallium scan remained positive in six of the patients at the end of therapy. One child sustained a significant amount of bone destruction from the disease, and had a strongly positive gallium scan throughout his hospital stay. All four patients with negative post-treatment gallium scans had osteomyelitis at sites of trabecular bone, while five of the six patients with persistent positive scans had osteomyelitis at sites of compact bone, implying an effect of the differences in bone repair on followup gallium scans. The authors concluded that although a negative gallium scan in the presence of a good clinical response to treatment helped support the determination of cure, the gallium scan cannot be used to define an end-point for therapy due to the number of cases in which the scan remains positive (42).

Although gallium imaging is an important tool in the diagnosis of osteomyelitis, there are several drawbacks: despite its high sensitivity for infectious processes, it possesses an unpredictable sensitivity for non-infectious inflammatory conditions and increased bone metabolism, as well as giving a higher radiation exposure to the patient than that necessary for bone scanning (69,70). The twenty-four hour delay required to obtain a satisfactory target to background ratio is also a detriment to the diagnosis of this disease in which the early initiation of treatment is essential to prevent irreversible bone damage (77). While more sensitive than the technetium-99m-MDP scan for osteomyelitis, a case of a falsely normal gallium image in a patient with classic acute osteomyelitis has been reported (24). Despite these problems, the addition of a gallium scan to a normal or equivocal bone scan in the evaluation of suspected osteomyelitis remains the diagnostic algorithm of choice.

3

METHODS

The records of the Yale-New Haven Hospital during the 28 month period from April 1982 through July 1984 were reviewed for all children sixteen years of age or younger who underwent a bone scan (technetium-99m-MDP) followed by a gallium-67-citrate scan within four days for evaluation of suspected osteomyelitis. Thirty-nine children fit these criteria, however the case records of two children were unavailable, the scintigraphs for one child could not be located, two children had been surgically treated between scans, and three children did not have adequate proof for a final diagnosis, leaving 31 children for analysis.

These children were divided retrospectively into those with acute osteomyelitis (8 cases) and those without osteomyelitis (23 cases). In the group with osteomyelitis the diagnosis was established either by surgical pathology and/or culture of the biopsy specimen (five cases), by subsequent roentgenologic changes of osteomyelitis along with localized bone tenderness and swelling with a favorable response to antibiotic treatment (two cases), or by positive blood culture, fever, multiple sites of localized bone

tenderness and swelling, and a favorable response to antibiotic therapy (one case). Although there were several cases with more than one suspected site of osteomyelitis, only one site per child, as proven above, was included in statistical analysis.

The second group, those without acute osteomyelitis, were confirmed by complete resolution without antibiotic therapy (9 cases), with only short term antibiotic therapy (1 to 16 days, mean = 7 days) (11 cases), or by serial negative roentgenologic examinations in cases in which long term antibiotic therapy was given for other reasons (two cases). The final case was proven by the surgical diagnosis of an alternate cause for the initial symptoms. These patients were followed for a period of three to 31 months to exclude the emergence of untreated or undertreated osteomyelitis. The final diagnoses are presented in table 1.

Bone scans were performed two to four hours following intravenous administration of approximately 200 uCi/Kg Tc-99m-Methylenediphosphonate*. Images were obtained on a large-field gamma camera. Views with pinhole-collimation were obtained when necessary. Gallium-67 images were performed 24-72 hours following intravenous administration of 70 uCi/Kg of radionuclide using a triple window large-

* Osteolite, New England Nuclear, North Ballerica, MA.

field camera equiped with a middle energy collimator.

The scintigraphs were reviewed and categorized in three stages by two experienced observers. The categorization was by consensus. The scintigraphic examinations were randomized and the only clinical information given was the suspected site of the lesion if known. First, the bone scans were reviewed; scans with focally increased activity were considered positive for osteomyelitis. Next, at a

Table 1. Distribution of Cases by Final Diagnosis

Final Diagnosis	Number of cases
Osteomyelitis	8
Cellulitis	5
Juvenille Rheumatoid Arthritis	3
Fracture	3
Septic Arthritis	1
Other Diagnoses*	11

*includes one case each of infected trochanteric bursa, diskitis, unspecified sterile arthritis, knee contusion, sinusitis, sepsis, granulomatous adenitis, neutropenia, decubitus ulcer, ideopathic knee effusion, and no pathology found.

separate session, the Ga-67 images were interpreted without reference to the bone scan, with focal areas of increased activity localized in bone considered positive for osteomyelitis. Finally, the gallium and bone scan images were viewed together; the criteria of combined scan positivity for osteomyelitis were either a pattern of focally increased gallium scan activity greater or equal to that in the same region of bone on bone scan, or a pattern of gallium uptake disparate to that seen on bone scan (61). A positive result was recorded for any scintigraph meeting these criteria, regardless of whether other explanations for uptake were also tenable.

The data were divided in several ways for analysis. Those children with the underlying complicating pathologic processes of bone violated by surgery or by fracture, juvenille rheumatoid arthritis, hemoglobin S-C disease, a penetrating wound, or an adjacent soft tissue infection were separated from those children without these complicating factors. In another separate analysis, children with suspected lesions in the axial skeleton or the femoral head or neck (central lesions) were separated from those with suspected peripheral osteomylitis.

The data were analyzed to determine the sensitivity and specificity of the bone scan alone, the gallium scan alone,

and of the interpretation of the combined bone and gallium images in the diagnosis of acute osteomyelitis in the study population as a whole and for each of the subdivisions. The two-tailed Fisher Exact test was used to compare both the sensitivity and specificity of each imaging agent and the combined bone and gallium images for the population subdivisions.

The effects of elapsed time between the onset of symptoms and day of imaging, and of antibiotic therapy prior to imaging, were also evaluated.

4

RESULTS

Table 2 details the interpretation of the Tc-99m-MDP and Ga-67 citrate scans for all children in the study (31 cases), those children with (11 cases) and without (20 cases) underlying complicating pathologic processes as defined above, those children with central suspected lesions (9 cases), and those with peripheral suspected lesions (20 cases). Since the combined sequential interpretation was the same as that for gallium alone in all patients in this study, only one value for both is listed in the results. The overall sensitivities and specificities for this series are shown in table 3.

The ten cases which were bone scan positive but did not have osteomyelitis included two cases of cellulitis, two cases of juvenille rheumatoid arthritis, three cases with fracture, one case with sinusitis, one case with an unspecified sterile arthritis, and one case where no pathology was found in the site of uptake.

Table 2. Results of Scintigraphic Imaging

	Osteomyelitis				Not osteomyelitis			
	Tc-MDP		Gallium		Tc-MDP		Gallium	
	+	-	+	-	+	-	+	-
Total Study Population	5	3	8	0	10	13	7	16
With Underlying Pathology*	3	0	3	0	6	2	3	5
Without Underlying Path.	2	3	5	0	4	11	4	11
Central** Lesions	1	0	2	0	3	4	0	7
Peripheral Lesions	4	3	6	0	7	7	7	7

*Defined as bone violated by surgery or fracture, juvenille rheumatoid arthritis, sickle-cell hemoglobinopathy, soft tissue infection, or penetrating wound.

**suspected site of osteomyelitis in the axial skeleton, femoral head or neck.

Table 3. Sensitivity and Specificity of Scintigraphic Imaging for the Total Study Population

	Sensitivity	Specificity
Tc-99m-MDP	0.625	0.565
Gallium and Sequential	1.00	0.695

Of the three cases which were bone scan negative but had acute osteomyelitis, the first was a three week old infant who was imaged seven days after the onset of irritability, swelling, erythema, and disuse of the left upper and lower extremities and who was subsequently shown to have osteomyelitis of the elbow. The second was an eight day old neonate who was imaged two days after the onset of tenderness and disuse of the left lower extremity and who was later proven to have osteomyelitis of the left humeral head; the final case was that of a two year old child who was scanned six days after the onset of fever, erythema, and swelling of the right shoulder and who was proven to have osteomyelitis of the proximal humerus.

The seven cases which were positive on gallium and sequential interpretation but did not have osteomyelitis included two cases of cellulitis, two cases of juvenille rheumatoid arthritis, two fractures, and one ideopathic knee effusion.

The sensitivities and specificities of the scans for those children with and without underlying complicating pathology as defined above are presented in table 4. The differences in sensitivity for bone, gallium, and combined scanning, and the differences in specificity for the gallium and combined studies were not statistically significant. However, the

difference in specificity for the bone scan with versus without underlying pathology was significant (p=0.039).

Table 4. Comparison of Sensitivity and Specificity Between Cases With and Without Underlying Pathology

	With Underlying Pathology		Without Underlying Pathology	
	Sens.	Spec.	Sens.	Spec.
Tc-99m-MDP	1.00	0.25	0.40	0.733
Gallium and Sequential	1.00	0.625	1.00	0.733

Table 5. Comparison of Sensitivity and Specificity Between Cases With Central and Peripheral Suspected Lesions

	Central Suspected Lesions		Peripheral Suspected Lesions	
	Sens.	Spec.	Sens.	Spec.
Tc-99m-MDP	1.00	0.57	0.57	0.50
Gallium and Sequential	1.00	1.00	1.00	0.50

The sensitivities and specificities for central and peripheral suspected lesions are presented in table 5. The difference in specificity for the gallium and sequential studies in a central versus peripheral suspected lesion was

statistically significant ($p=0.046$), however the difference in sensitivities, and the difference in specificity for the bone scan, were not statistically significant.

The data were examined for a correlation between the number of days between the onset of symptoms and the time of technetium-99m-MDP and gallium imaging. This interval ranged from one to 36 days (mean 11.0) for the bone scan, and from 3 to 40 days (mean 12.7) for the 24 hour gallium imaging. The three false negative bone scans were performed within seven days of the onset of symptoms. The bone and gallium scans that were positive in the absence of osteomyelitis were evenly distributed and showed no correlation with the time elapsed before imaging.

The cases were further divided by the number of days of antibiotic therapy received before imaging, presented in table 6. There was no significant effect of antibiotic therapy on the sensitivity or specificity of either scan in this series.

Table 6. Antibiotic Therapy Prior to Imaging in Cases of Osteomyelitis

	No Prior Rx	Prior Rx
Total Tc-99m-MDP	3	5
Total Gallium	2	6
Tc-MDP Negative with osteomyel.	2	1

5

DISCUSSION

Previous studies of the use of sequential technetium-99m-MDP and gallium imaging in the diagnosis of osteomyelitis have reported sensitivities ranging from 72 to 100 percent and specificities ranging from 25 to 100 percent (32, 46, 47, 64, 66, 61). This large range is primarily due to differences in study populations and methods of arriving at a final diagnosis. The children in this study are a select population in that they received both a bone scan and a gallium scan in an institution where many children receive only a bone scan in the evaluation of suspected osteomyelitis. There are several situations in which both modalities are used at the Yale-New Haven Hospital: patients with suspected lesions at sites of other underlying pathology, eg. fracture; patients in whom the bone scan is normal or equivocal but clinical suspicion of osteomyelitis is high; finally, the suspicion of osteomyelitis in the neonate is routinely evaluated by both Tc-99m-MDP and gallium imaging. These preselection criteria create a population which has a higher probability of other underlying disease and more complicated clinical history

than the general population of children with suspicion of osteomyelitis, therefore the sensitivity and specificity data obtained in this study apply only to the more select population of "difficult" cases.

Inspection of the cases of osteomyelitis missed by the bone scan reveals several interesting findings. Two of these three children are the only neonates in this series. This finding supports previous work by Ash *et al* and Mok *et al* in which only 42% to 70% of neonates with confirmed osteomyelitis had an abnormal bone scan (4,53). This finding, however, is contrary to a more recent study by Bressler *et al* which suggests a bone scan sensitivity of 100% in neonates with osteomyelitis (11). The second similarity between these three cases was the time elapsed from the onset of symptoms to bone scan imaging: two, six, and seven days. Only one other child with osteomyelitis was imaged within seven days, with correct diagnosis by bone scan. This finding agrees with both experimental work indicating that the bone scan is less sensitive early in the course of osteomyelitis (20, 29, 58, 60), and clinical investigation in which negative bone scans in the presence of osteomyelitis were followed by positive scans later in the course of the disease (68, 32, 25).

Examination of the causes of positive gallium interpretations in the absence of osteomyelitis also merits attention. Uninfected fracture as a cause for a falsely positive gallium scan has been reported (46, 51, 61), and gallium uptake has been evaluated experimentally in uninfected fractures (12). Two cases of positive gallium scans with uninfected fracture in this series support the contention that gallium uptake at fracture sites may be high enough to cause the false diagnosis of infection.

The significantly lower specificity of the bone scan in those cases with underlying complicating pathology is not unexpected. Variably increased technetium-99m-MDP uptake in the absence of osteomyelitis is expected in cases of fracture or surgically violated bone (3 cases), inflammed joints(discussed below) (2 cases), and may be seen with the increased bloodflow associated with an adjacent soft tissue infection (one case) (22,35).

The uptake of gallium in bones with increased bone turnover as noted in the two cases of fracture above can be related to the location of the lesions. Experimental work has shown that the higher contrast of technetium-99m-MDP as compared to gallium in situations with increased bone turnover is not due to less relative uptake of gallium in active bone, rather to a higher gallium background in the adjacent soft

tissues (12). The significantly lower specificity of gallium in peripheral compared to central lesions may be partially due to a higher apparent uptake by active bone in the periphery caused by a smaller amount of adjacent soft tissue to provide a source of background activity. Thus both cases of fractured extremities appeared 'hot' on gallium scan, while a vertebral compression fracture of T6-T7 with increased technetium-99m-MDP uptake appeared normal on gallium scan. Another contributing factor to the decreased specificity of the gallium scan in the extremities may be the increased frequency of cellulitis and inflammatory joint disease in the periphery in this series and difficulty in anatomically differentiating soft tissue and joint from bone uptake. This problem of anatomic localization is especially difficult in children since the structures being examined are small compared to system resolution. Motion artifact is also often unavoidable.

The distinction between osteomyelitis and bone infarction in children with sickle cell disease on the basis of bone scan results may be unreliable, with both processes giving rise to similar scintigraphic findings of focally increased or decreased uptake (1,33,35,49,50). The use of gallium imaging as an adjunct to the bone scan was suggested for this clinical dilemma (3), and recently Amundsen and associates described a series in which sequential scanning

was used in patients with sickle cell hemogloblinopathies in whom osteomyelitis was suspected (1). With the criteria for osteomyelitis consisting of either decreased or normal uptake on bone scan along with increased uptake on gallium scan in a congruent spatial distribution, or of increased uptake on both scans in an incongruent distribution, the sensitivity for diagnosing osteomyelitis was four out of four episodes, while the accuracy of diagnosing infarct alone was 16 of the 18 episodes.

The clinical problem of infection versus infarction was observed in one patient in our series. An eight year old girl with SC hemoglobinopathy presented with fever and pain in the left thigh of one and a half weeks duration. Scintigraphic studies fell into the category of incongruent spatial distribution as decribed by Amundsen. Surgical findings were consistent with osteomyelitis, and Salmonella was subsequently cultured from the surgical specimen.

The effect of prior antibiotic treatment on radionuclide imaging for osteomyelitis has been evaluated in the past. No decrease in the sensitivity of the gallium scan has been shown with less than 10 days of antibiotic therapy in a clinical setting (61), and no decrease in the sensitivity of the bone scan has been shown for up to 8 weeks of antibiotic

therapy in an experimental setting (30). The lack of correlation between the duration of antibiotic treatment and sensitivity of the scans in this study supports these previous findings.

Periarticular localization of radionuclides has been noted in adults with active rheumatoid arthritis both for technetium-99m-MDP (17), and for gallium (17,52). Three cases in this series of children were given the final diagnosis of active joint inflamation secondary to JRA to account for the presenting signs and symptoms. Two of these three children had both positive bone and gallium scans, while the third had normal scans in the region of interest. Pathological examination of joints involved by JRA has shown subsynovial tissues to be hyperemic and edematous (15). The ossifying blood vessel buds growing out from the epiphyseal center are irregular in very young children with JRA, and bony overgrowth of the juxtaarticular epiphysis may eventually occur (13). Progressive erosion and destruction of the articular cartilage and juxtaarticular bone may be seen, however this generally occurs much later than in adult rheumatoid arthritis (13,15). The hyperemia of early JRA and additional increased bone turnover of late JRA will cause an increase in the technetium-99m-MDP uptake by the juxtaarticular bone similar to that observed in adult

rheumatoid arthritis (39). The increased gallium uptake noted in these two patients can be explained by several mechanisms. The synovial fluid of an affected joint accumulates an average of 15 to 20,000 WBC/mm3 (15) and may reach as many as 80 to 100,000 WBC/mm3 (5,82), 75 percent of which are polymorphonuclear leukocytes(PMNs). Gallium is retained by binding to lactoferrin released into the synovium and synovial fluid by the PMN secondary granules (8,38,80). The difficulty in resolving uptake in the hypertrophied synovium from the adjacent bone in children increases the apparent juxtaarticular uptake of gallium. Juxtaarticular uptake can also be explained on the basis of increased blood flow and turnover in the bone, utilizing the bone-seeking behavior of gallium along with the increased apparent bone contrast in the extremities as discussed above. As a result of these mechanisms the differentiation of acute osteomyelitis from an inflammed joint of JRA can be difficult in the pediatric population.

6

CONCLUSIONS

The diagnosis of acute osteomyelitis in children remains a difficult clinical dilemma, increased when the situation is complicated by underlying pathology or a non-diagnostic or questionable bone scan, as in the population analyzed above. The bone scan may be less sensitive early in the course of the disease and in the neonate. Although the specificity of the gallium scan is not perfect, with fracture, juvenille rheumatoid arthritis, and cellulitis contributing to false interpretation as osteomyelitis, sequential interpretation through the addition of a gallium scan after Tc-99m-MDP bone imaging increases both the sensitivity and specificity of the scintigraphic diagnosis of acute osteomyelitis in children.

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